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09/671,995	09/29/2000	Ravi V. J. Chari	104322.198 US1	2588

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HALE & DORR LLP
THE WILLARD OFFICE BUILDING
1455 PENNSYLVANIA AVE, NW
WASHINGTON, DC 20004

EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	16

DATE MAILED: 05/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/671,995	CHARI, RAVI V. J.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32,40,41 and 44-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,41 and 44-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-32,40,41 and 44-89* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,9* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *14* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The election with traverse filed November 7, 2001 in Paper No. 13 is acknowledged and has been entered. Applicant has elected the invention of group 2, claims 40, 41, and 44-89, drawn to composition and a kit.

2. The supplemental election with traverse filed February 14, 2002 in Paper No. 14 is acknowledged and has been entered. Applicant has elected the species of invention wherein the composition or kit comprises an immunoconjugate comprising the humanized antibody N901 or a fragment thereof and a maystansinoid and wherein the composition or kit further comprises paclitaxel.

3. Claims 1-32, 40, 41, and 44-89 are pending in the application. Claims 1-32 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper Nos. 13 and 14.

Election/Restrictions

4. Applicant's elections with traverse in Paper Nos. 13 and 14 are acknowledged. The traversal is on the ground that searching and examining the inventions of group 1 and group 2 would not constitute serious burden, since the search required for examination of the elected group 2 would encompass the search required for examination of group 1. This is not found persuasive because contrary to Applicant's assertion, the searches required for examination of groups 1 and 2 are not co-extensive. Accordingly, a different search is required for examination of groups 1 and 2, and therefore, searching and examining both inventions would constitute serious burden. Thus, the restriction requirement is deemed proper and is made FINAL.

Nevertheless, claims 40, 41, and 44-89 are directed to product. Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86),

claims 1-32, directed to the process of using the product, which have been withdrawn from consideration as a result of the restriction requirement, will be subject to rejoinder, at Applicant's request, once claims 40, 41, and 44-89 are directed to an allowable product. However, in accordance with the Official Gazette notice, *supra*, process claims, which do not depend from or otherwise include all the limitations of an allowable product, will NOT be rejoined.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because a non-initialed and non-dated alteration has been made to the declaration. See 37 CFR § 1.52(c).

Claim Rejections - 35 USC § 112

6. The specification is objected to and claims 52 and 74 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

Claims 52 and 74 are drawn to a composition and a kit comprising an immunoconjugate comprising a humanized antibody, which is designated N901 or C242.

It is unclear if a cell line that produces an antibody having the exact structural and chemical identity of the humanized antibody to which the claims refer is known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to a hybridoma cell line producing the monoclonal antibody from which the humanized antibody to which the claims refer is derived, it would not be possible to practice the claimed invention, because it would not be possible to make the

either the monoclonal or the humanized antibody. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics (Fundamental Immunology, 3rd ed., William E. Paul, M.D. ed., 1993, page 242). Therefore, it would require undue experimentation to reproduce the claimed antibody. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph (see 37 C.F.R. 1.801-1.809).

It appears that Applicant has not disclosed the deposit of hybridoma cell lines that would reproduce the humanized antibody species, N901 or C242, or the monoclonal antibodies from which the humanized antibodies were derived.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by Applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

If the original deposit is made after the effective filing date of an application for patent, the Applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 48-53, 56, 70-75, and 78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 48, 49, 52, 70, 71, and 74 are vague and indefinite because the claims recite the term "fragment thereof". Recitation of the term renders the claims vague and indefinite because it cannot be ascertained whether the claims require the fragment of the antibody to be able to bind the antigen to which the antibody binds. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 50, 51, 72, and 73 are vague and indefinite because the claims recite the phrase "capable of binding". Recitation of the phrase renders the claims vague and indefinite because the claims do not recite the condition under which the claims require the antibody or fragment thereof to be capable of binding the antigen expressed by a cancer cell or a CD56 antigen. Furthermore, it is unclear whether the claims require the antibody or fragment thereof to actually be able to bind the antigen or merely have the

potential to bind; and it is not clear whether the claims require the antibody or fragment thereof to bind specifically or merely non-specifically. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 52 and 74 are indefinite because the claims use of the designations "N901" and "C242" as the sole means of identifying the humanized antibodies to which the claims refer. The use of laboratory designations only to identify a particular antibody renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct antibodies. Amendment of the claims to include the name of the depository and the accession number of the biological deposit, i.e., hybridoma that produces the antibodies to which the claims refer can obviate this rejection, because the deposit number is unique identifier that unambiguously defines a given hybridoma and the antibody produced thereby.

Claims 52 and 74 are indefinite because the claims recite the limitation "wherein the monoclonal antibody or fragment thereof is humanized N901 or humanized C242". Recitation of the limitation renders the claims indefinite because humanized N901 and humanized C242 antibodies are not fragments of antibodies, nor are they monoclonal antibodies in the strictest sense. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 53 and 75 are indefinite because the claims recite the limitation "wherein the monoclonal antibody or fragment thereof is Fv, Fab, Fab', or $F(ab')_2$". Recitation of the limitation renders the claims indefinite because a monoclonal antibody is not a Fv, Fab, Fab', or $F(ab')_2$. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 56 and 78 are vague and indefinite because the claims recite the term "a taxane mechanism". Recitation of the term renders the claims vague and indefinite because it is unclear by which mechanism the claims require the compound to act; it is also unclear how and upon what subject matter, the claims require the compound to act.

Claim Rej cti ns - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 40, 41 and 44-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu, et al (*Proceedings of the National Academy of Sciences USA* **93**: 8618-8623, 1996; Form PTO-1449, citation K) in view of Mendelsohn (*Clinical Cancer Research* **3**: 2703-2707, 1997; Form PTO-1449, citation Y) and Hortobagyi (*Oncology* **11**: 11-15, 1997).

Claims 41 and 66-89 are drawn to a kit comprising at least one chemotherapeutic agent and at least one immunoconjugate, wherein said immunoconjugate comprises a humanized antibody, namely C242 or N901, conjugated to an anti-mitotic agent. Claims 40 and 44-65 are drawn to a composition comprising a chemotherapeutic agent and further comprising an immunoconjugate, wherein said immunoconjugate comprises a humanized antibody, namely C242 or N901, conjugated to an anti-mitotic agent.

Liu, et al teach an immunotoxin comprising a humanized antibody, namely C242 that is conjugated a maystansinoid, namely DM1 (page 8618, column 2). Liu, et al teach an isotype-matched immunoconjugate comprising humanized antibody, namely N901 that is also conjugated to DM-1 (page 8620, column 2). Liu, et al teach that the latter immunoconjugate does not bind COLO 205 cells; therefore, the immunoconjugate can be used as a negative control in experiments. Additionally, Liu, et al teach a chemotherapeutic agent, namely 5-fluorouracil (5-FU), which Liu, et al disclose is the standard chemotherapeutic drug used for treatment of colorectal cancer (page 8621, column 2). Liu, et al teach that 5-FU only slightly delayed tumor growth in a xenograft animal model of colorectal cancer, whereas treatment of the animals with the C242-DM1 conjugate rendered the animals tumor-free for more than 200 days, i.e., throughout the duration of the experiment (page 8621, column 2).

However, Liu, et al do not teach a kit. Furthermore, Liu, et al do not teach a composition of an immunoconjugate and a chemotherapeutic agent.

Mendelsohn teaches that combining a therapeutic chimeric antibody with a chemotherapeutic drug successfully eradicates well-established tumor xenografts that resist treatment with either agent alone (abstract). Mendelsohn discloses that combination regimens of the therapeutic chimeric antibody and doxorubicin, cisplatin, or paclitaxel are being investigated in clinical trials (abstract).

Hortobagyi teaches a rationale for combination therapy, emphasizing in particular, the efficacy and safety of combination therapy comprising the taxane, Docetaxel (abstract). Hortobagyi teaches that Docetaxel has an effect upon cells that are resistant to other chemotherapeutic agents, such as 5-FU. Hortobagyi discloses many different chemotherapeutic agents, including paclitaxel, vinorelbine, etoposide, cisplatin, and doxorubicin, and teaches that combinations of Docetaxel and other agents have been shown to be highly active in preclinical mode (page 12). Moreover, Hortobagyi teaches that synergies, or at least additive effects, were observed in studies with two- and even three-drug combinations. Hortobagyi concludes, "[t]he challenge is not only to find effective combinations, strategies, and regimens, but also to determine the optimal role for [docetaxel] in relation to many other active agents in development today" (page 14).

Given the teachings of Liu, et al, in view of the teachings of Mendelsohn and Hortobagyi, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to manufacture a kit comprising at least one, if not several chemotherapeutic agents currently in development and widely known in the art, including but not necessarily limited to Docetaxel, Paclitaxel, Vinblastine, Navelbine, dolastatin, cryptophycin, cisplatin, epothilone, Etoposide, Camptothecin, and the C242-DM1 immunoconjugate of Liu, et al, together with the isotype-matched N901 immunoconjugate for use as a negative control, because kits provide greater ease of use, convenience, and uniformity. One skilled in the art would have been motivated at the time the invention was made to manufacture such a kit, because the kit could be used to find effective combinations, strategies, and regimens, and to determine the

optimal roles for one agents in relation to the others. For example, given the teachings of Liu, et al, one of ordinary skill in the art would have been motivated to determine if a combination of the immunoconjugate of Liu, et al and one or more of the chemotherapeutic agents be more effective than any of the agents alone, since both Mendelsohn and Hortobagyi teach that combination therapy is often more effective than monotherapy because synergistic or additive effects are often observed in the former. Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art to make a composition comprising one or the other immunoconjugates of Liu, et al and further comprising at least one of the chemotherapeutic agents currently under development and widely known in the art. One of ordinary skill in the art would have been motivated to use the kit to find the most effective combination of agents and to determine the optimal roles of one of the agents in relation to the others, because there had been a long-felt need for more efficacious antitumor therapies and for a greater understanding of the pharmacology of combination therapies.

Conclusion

11. No claims are allowed.

12. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Each of the cited references, which were not used as a basis of rejection in this Office Action, disclose immunoconjugates, antibodies, chemotherapeutic agents, therapeutic regimens, doses, and schedules, and methods for making therapeutically useful antibodies and immunoconjugates, all of which are pertinent to Applicant's disclosure. Each of the cited references may be referred to during subsequent prosecution to support the obviousness of the claimed invention under 35 USC § 103, and therefore each may also be used as a basis of additional rejections.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is

(703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
May 6, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600